EPIDEMIOLOGY OF BLADDER CANCER

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Each year in the United States, approximately 49,000 persons develop cancer of the urinary bladder and 9700 die from the disease.[182] Bladder cancer accounts for 7% of all new cases of cancer among men and 3% of cases among women, as well as 2% of cancer deaths among men and 1% among women.

DESCRIPTIVE FACTORS

Histopathology and Anatomic Distribution

More than 98% of bladder cancers diagnosed in the United States are histologically confirmed (Devesa, unpublished data, and the Surveillance, Epidemiology, and End Results (SEER) program[224]). Most of these are transitional cell carcinomas (93%); 2% are squamous cell carcinomas, and 1% are adenocarcinomas. About 43% do not have a subsite within the bladder specified, and 13% arise in more than one subsite. Of bladder cancers for which a single subsite is specified, most occur on one of the bladder walls, with three times as many on the lateral walls (40%) as on the anterior (3%) or posterior (11%) walls combined. Less common subsites include the ureteric orifice (17%),

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followed by the trigone, dome, and neck (13%, 9%, and 7%, respectively).

Geographic Variation

Internationally, incidence rates of bladder cancer vary about tenfold.[150] High rates occur in western Europe and North America; relatively low rates are found in eastern Europe and several areas of Asia (Fig. 1). The geographic variation may reflect local practices in registration of "benign" tumors or "papillomas" as cancer, although rates reported by registries that include these categories are not consistently high compared with rates reported by other registries. Within the United States, bladder cancer incidence (Table 1) and mortality[118, 166] are higher in parts of the northeast and upper midwest and generally lower in the south.

In the United States, urban areas had higher mortality rates than rural areas, but these differences have diminished.[10, 68] Recent international incidence data indicate that urban excesses persist in many other countries.[150]

Sex, Race, and Age

Cancer of the bladder occurs primarily among white men (Table 2). In most racial groups, the male:female rate ratio is at least 3:1, approaching 4:1 among whites. The incidence rate among black men is about 50% of that among whites. Rates are somewhat lower among Asian and Hispanic groups than among blacks, and very low among American Indians. Social class has little impact on the risk of bladder cancer and does not explain the black-white difference in incidence.[48, 114, 125]

Incidence and mortality rates rise sharply with age (Figs. 2 and 3); about two thirds of cases occur among persons 65 years of age and older. A higher incidence among whites compared with blacks occurs over the entire age range (see Fig. 2). A higher mortality in whites than in blacks is seen only among men 65 years of age and older (see Fig. 3). Among women, higher mortality in blacks than in whites is apparent at all ages except the oldest. Lifetime risk of developing bladder cancer is 2.8% for white men; for black men, white women, and black women, the risks are 0.9%, 1.0%, and 0.6%, respectively.[179]

Stage of Disease

The stage of bladder cancer at diagnosis varies markedly by age, sex, and race, with young white women diagnosed with least advanced disease. The proportion localized at diagnosis declines with age; 82%

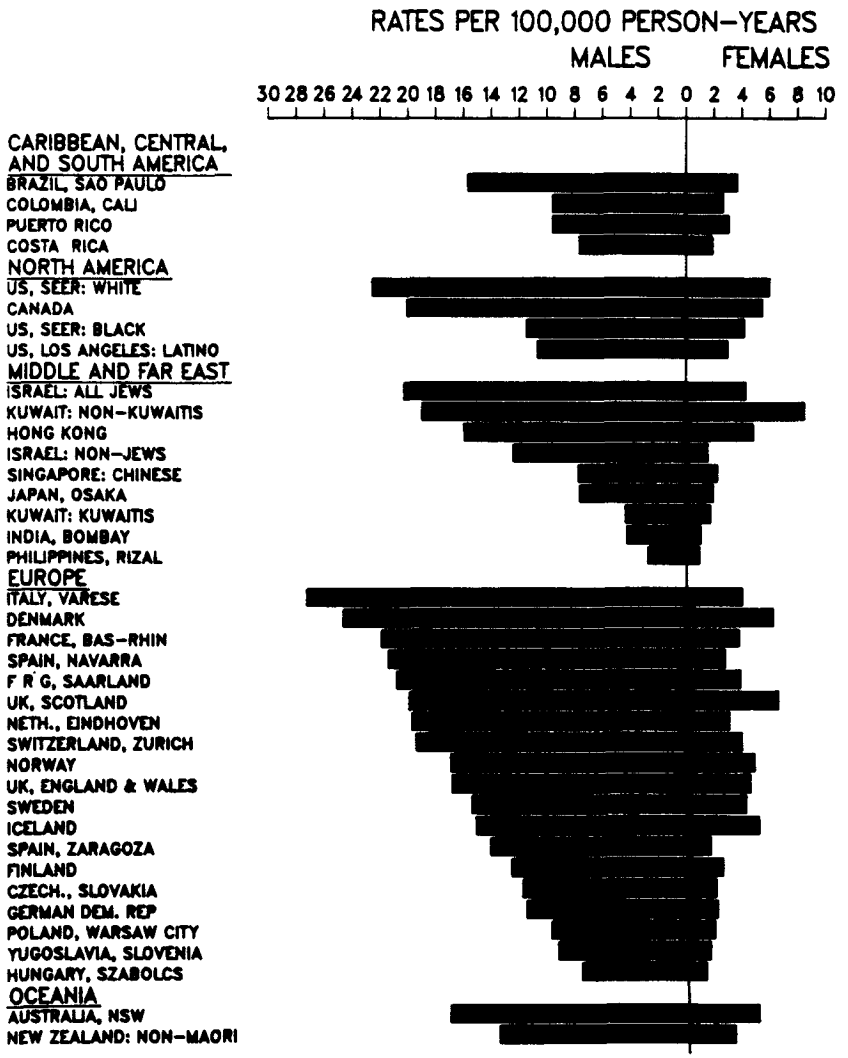

Figure 1. International variation in age-adjusted (world standard) bladder cancer incidence rates per 100,000 person-years by sex, 1978 to 1982. (*Data from* Muir C, Waterhouse J, Mack T, et al (eds): Cancer Incidence in Five Continents, vol. 5. IARC Publication Number 88. Lyon, International Agency for Research on Cancer, 1987.)

of patients aged 40 to 44 years present with local disease, whereas 61% of patients over 84 years do so (Devesa, unpublished data from the SEER program). The proportion localized is 73% among white men, 69% among white women, 59% among black men, and 49% among black women. The higher incidence among whites as compared with blacks is limited to localized cases, with blacks and whites having a similar risk of more advanced tumors.[175]

Table 1. BLADDER CANCER INCIDENCE AMONG WHITES BY AREA AND SEX, US SEER PROGRAM, 1975–1985*

Geographic area	Males		Females	
	Cases	Rate†	Cases	Rate†
Detroit	5127	33.5	1793	8.4
Hawaii	372	33.5	87	6.9
Connecticut	5153	32.7	1968	8.9
Seattle	3772	30.4	1322	8.0
San Francisco	3925	28.9	1536	7.9
Iowa	4686	28.3	1599	6.7
Atlanta	1312	28.3	477	6.7
Utah	1173	22.3	352	5.2
New Mexico	1064	19.9	348	5.3
All areas	26584	29.6	9482	7.6

**Data from* Devesa, unpublished data from the Surveillance, Epidemiology, and End Results (SEER) program.

†Rates per 100,000 person-years, age-adjusted by the direct method using the 1970 US population standard.

Time Trends

From 1969-1971 to 1984-1986, incidence rose 22% to 38%, depending on race and sex. Increases in incidence were greater during the 1970s than during the 1980s and mortality fell 16% to 23% (Fig. 4).

The observed increases in incidence may be explained partly by changes in diagnostic practice. The proportion of bladder tumors classified as "carcinoma in situ" increased from less than 1% in 1969 to 1971 to more than 7% during the 1980s[41] (Devesa, unpublished data from the SEER program). Much of the observed rise in incidence

Table 2. BLADDER CANCER INCIDENCE BY RACIAL/ETHNIC GROUP AND SEX, US SEER PROGRAM, 1975–1985*

Racial/ethnic group	Males		Females	
	Cases	Rate†	Cases	Rate†
White	26584	29.6	9482	7.6
Black	1071	15.1	533	5.6
Chinese‡	157	13.9	48	3.9
Japanese‡	214	12.6	98	4.4
Hispanic§	178	11.3	61	3.3
Hawaiian‖	44	10.6	30	6.0
Filipino‡	72	5.9	21	3.0
American Indian§	10	3.5	1	0.4

**Data from* Devesa, unpublished data from the SEER program.

†Rates per 100,000 person-years, age-adjusted by the direct method using the 1970 US population standard.

‡Residents of San Francisco–Oakland and Hawaii.

§Residents of New Mexico.

‖Hawaii only.

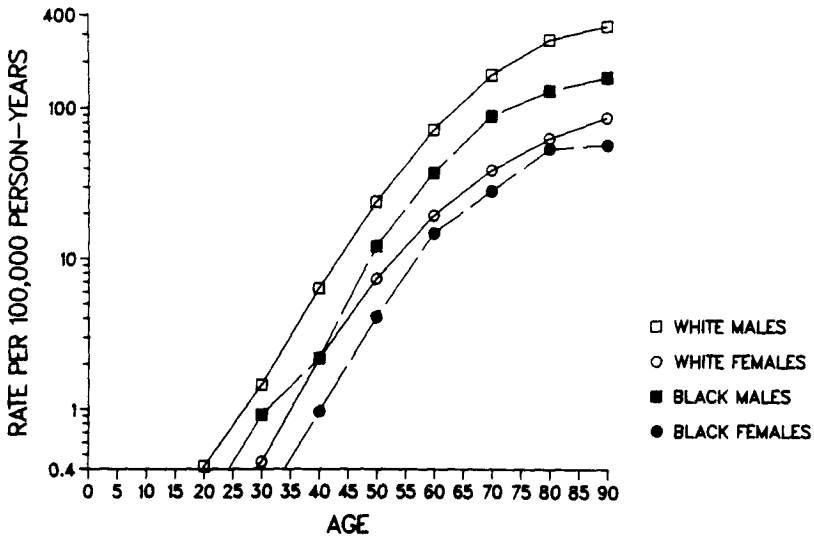

Figure 2. Age-specific incidence rates for bladder cancer in the US SEER program by race and sex, 1975 to 1985. (*Data from* the SEER program, unpublished data.)

appears to be a result of an increase in the incidence of localized bladder cancer (including in situ), which rose from 10.3 per 100,000 in 1975 to 1978 to 11.8 per 100,000 in 1982 to 1985 (Devesa, unpublished data from the SEER program). This increase was accompanied, however, by

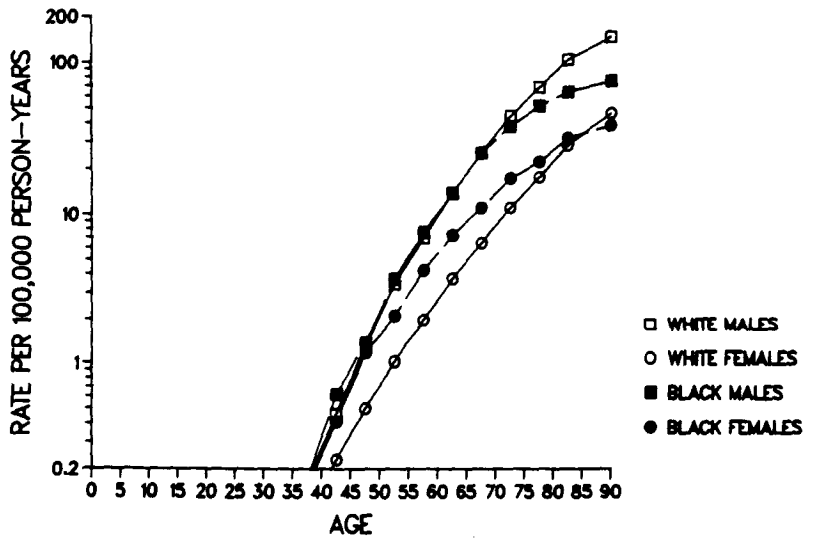

Figure 3. Age-specific mortality rates for bladder cancer in the total United States by race and sex, 1975 to 1985. (*Data from* the National Center for Health Statistics.)

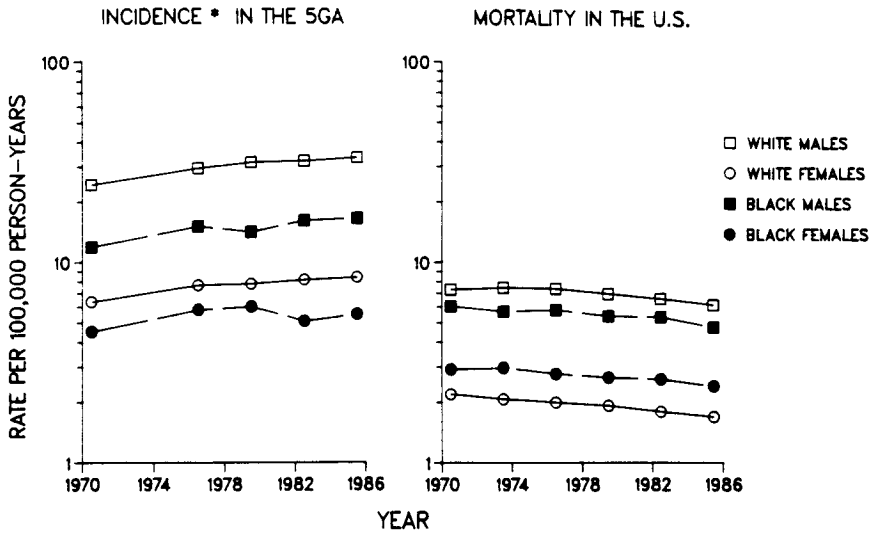

Figure 4. Trends in age-adjusted (1970 standard) bladder cancer incidence and mortality rates in the United States by race and sex, 1969 to 1986. Incidence data not available for 1972 to 1974. (Based on unpublished data from the five geographic areas (5GA) included in the 1969 to 1971 Third National Cancer Survey (TNCS), the SEER program, and the Connecticut Tumor Registry.[49])

a decrease in the incidence of unstaged bladder cancer (1.7 to 0.7 per 100,000), suggesting that some of the apparent increase in localized disease was the result of a reduction in the frequency of unstaged cases. Incidence of regional- and distant-stage bladder cancer remained virtually constant.

Survival

The 5-year relative survival of bladder cancer patients ranges from 87% for those diagnosed with localized disease to 9% for those with distant disease (Fig. 5). Whites with localized or regional disease have a better prognosis than blacks. White men with regional disease have a better prognosis than white women. Black women with localized disease have a worse prognosis than black men. Among cases with distant disease, survival varies little by race or sex. Overall black-white survival differences are only partly explained by differences in stage at diagnosis; racial disparities persist after adjustment for stage, histologic type, grade, and socioeconomic status.[70, 161]

Survival among patients with bladder cancer has increased more than 50% since the early 1960s.[155] In the period from 1974-1976 to 1980-1985, 5-year survival increased more among blacks (47.0% to 56.1%) than among whites (73.3% to 77.7%).

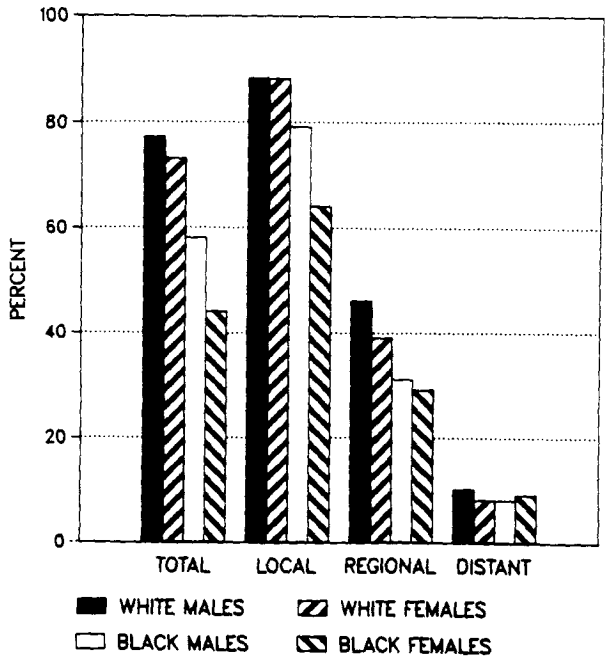

Figure 5. Five-year bladder cancer relative survival rates by stage, sex, and race. (*Data from* the National Cancer Institute, 1989.)

RISK FACTORS

Occupation

The study of occupational causes of bladder cancer gained momentum in the 1950s with the identification of bladder cancer hazards in the British dyestuffs and rubber industries.[24, 25] Numerous subsequent studies have identified approximately 40 high-risk occupations. Despite prodigious efforts, epidemiologists remain uncertain of the exact level of risks involved. Typically, a small number of workers are studied and their risk of bladder cancer is less than twice that expected. Further, many reported associations are not consistently found.[187] Strong evidence of increased risk is apparent for very few occupations: dye worker, aromatic amine manufacturing worker, leather worker, rubber worker, painter, truck driver, and aluminum worker.

Dyestuffs Workers and Dye Users

In 1895, Rehn first suggested that men employed in the dyestuffs industry had increased risk of bladder cancer. In 1954, Case et al[25] showed that dyestuffs workers in England and Wales had a 10 to 50 fold increased risk of death from bladder cancer due to exposure to

two aromatic amines, 2-naphthylamine and benzidine. Exposure to aniline did not affect risk, and 1-naphthylamine apparently affected risk only because it was contaminated by 2-naphthylamine.

Dyestuffs workers in northern Italy[44, 174] experienced increased risk from exposure to 2-naphthylamine and benzidine. The ratios of observed to expected bladder cancer mortality were 13, 34, and 71 for dyestuffs workers employed 10 years or less, 11 to 20 years, and more than 20 years, respectively. Dyestuffs workers involved in fuchsin and safranine T manufacturing also experienced high mortality (observed/expected = 62.5), which may have been the result of exposure to two precursors, o-toluidine and 4,4'-methylene bis(2-methylaniline).

The mean time from start of exposure to death was 25 years, with a range of 12 to 41 years. Risk was greatest for workers who started before age 25 years (observed/expected = 200.0). Risk also decreased after exposure ceased, although no trend of decreasing risk with increasing time since last exposure was observed.

The increased risk among dyestuffs workers has also been observed in case-control studies,[12, 109, 145, 153, 169, 171, 210] with relative risks ranging from 1.7 to 8.8. Data from the United Kingdom indicate that bladder cancer risk among dyestuffs workers has been reduced since the introduction of protective measures and the subsequent banning of the industrial use of 2-naphthylamine and benzidine in 1950 and 1962, respectively.[12, 145]

Users of finished dyes also may have an increased risk of bladder cancer, but the evidence is not as persuasive as that for dyestuffs manufacturing workers. Kimono painters, many of whom ingest benzidine-based dyes by licking the brush, had seven times the expected rate of bladder cancer.[223] Coarse fishermen who use chrysoidine azo dyes to stain maggot bait have been reported to have an increased risk of bladder cancer (relative risk = 3.0 for fishermen who used bronze dyes for 5 or more years).[192] Canadian dyers of cloth were reported to have a relative risk of 4.6,[171] and British textile dyers with more than 20 years employment had a relative risk of 3.4,[2] but two other studies found no excess risk for dye users.[23, 187]

Aromatic Amine Manufacturing Workers

Workers outside the dyestuffs industry have been exposed to 2-naphthylamine, benzidine, and a third bladder carcinogen, 4-aminobiphenyl, notably workers in chemical manufacturing.[93] A fourfold risk was observed among chemical workers in the United States exposed to 2-naphthylamine.[177] When excess bladder cancer was seen among workers involved in the commercial preparation of 4-aminobiphenyl, production ceased, averting widespread use of this aromatic amine.[93] In a cohort of workers at a benzidine manufacturing facility, an overall excess of bladder cancer cases was apparent (standardized incidence ratio [SIR] = 343).[127] Risk was greatest among those in the highest exposure category (SIR = 1303); little or no excess was observed for those in the low or medium exposure categories. Corresponding to the

introduction of preventive measures in the plant, a reduction in risk was observed for those first employed in 1950 or later compared with those first employed in 1945–49.

Two structural analogues of benzidine, MDA (4,4'-methylenedianiline), and MBOCA (4,4'-methylene-bis[2-chloroaniline]), are carcinogenic in animals,[178] and possibly in humans as well. MDA, a curing agent for certain resins, was associated with a threefold elevation of proportional mortality from bladder cancer.[178] MBOCA, a curing agent used in the manufacture of rigid plastics, has been suggested as the exposure responsible for two noninvasive papillary tumors of the bladder in workers in a MBOCA production plant, although no invasive bladder tumors have been identified in the cohort.[213] Manufacturing of another dyestuffs intermediate, 4-chloro-o-toluidine (4-COT), has been associated with excess bladder cancer mortality in a cohort of chemical workers in Germany (relative risk = 72.7).[193]

Rubber Workers

Antioxidants containing 2-naphthylamine were used in the rubber and electric-cable manufacturing industries in Great Britain until 1949.[7, 163] Case and Hosker[24] observed a twofold bladder cancer mortality risk, but only among British rubber workers employed before 1950.

Some studies of rubber workers in the United States[26, 47, 140] showed increased risk, but less than that seen among workers in Britain or Italy[157]; some studies found no excess risk.[99, 109, 124, 145] In the US rubber industry, workers were seldom exposed to 2-naphthylamine[26] but were exposed to another antioxidant, phenyl-β-naphthylamine (PBNA), which can be metabolized to 2-naphthylamine.[93]

Leather Workers

Leather workers experienced an increased risk of bladder cancer in at least ten studies,[8, 37, 45, 63, 77, 117, 145, 180, 210, 220] but leather tanners in two studies did not.[52, 197] The relative risk has varied from 1.4 to 6.3, with "leather worker" defined differently among the studies. Increased risks have been seen for shoe makers and shoe repairers,[63, 220] for workers in leather products manufacturing[45] or, more broadly, for workers exposed to leather or leather products.[37, 117, 145]

Leather workers are exposed to leather dust and to dyes, their solvents, and unreacted intermediates.[171] The exposure responsible for the increased risk among leather workers is not known; however, Cole et al[37] observed that the excess was related to cutting, assembling, finishing, and related processes. Marrett et al[117] found risk to be slightly higher for workers with possible exposure to leather dust as compared with other types of leather exposure.

Painters

Painters have had elevated bladder cancer risk in many studies,[31, 37, 46, 69, 77, 99, 109, 116, 120, 133, 145, 152, 187, 220] but not all.[55, 145] Typically, the overall

relative risks have been 1.2 to 1.5, and higher for those employed 20 years or more or before 1930 (3.0 to 4.1).[99, 187] Painters may be exposed to many known or suspected carcinogens in paints (e.g., benzidine, polychlorinated biphenyls, formaldehyde, and asbestos) and solvents (e.g., benzene, dioxane, and methylene chloride).[133]

Drivers of Trucks and Other Motor Vehicles

Excess risk of bladder cancer has been observed frequently among drivers of trucks, buses, or taxi cabs,[8, 31, 46, 50, 80, 94, 99, 114, 131, 176, 183, 184, 194] although one Swedish study found no elevation in risk for truck drivers.[116] Overall relative risks varied from 1.3 to 2.2, with relative risks for long-term drivers ranging from 2.2 to 12.0.[31, 80, 99, 183, 184, 194] In the largest study of bladder cancer among truck drivers, the trend in risk by duration of employment was most consistent for those first employed at least 50 years before observation[184] (Table 3). Although the etiologic agent has not been identified, one likely candidate is motor exhaust. Exhaust emissions contain polycyclic aromatic hydrocarbons (PAHs) and nitro-PAHs, which are highly mutagenic as well as carcinogenic in laboratory animals.[184]

Aluminum Workers

Wigle[214] noted an elevated incidence of bladder cancer among men in Quebec Province of Canada near the aluminum refining industry. The link was confirmed in two cohort studies of aluminum smelter workers[65, 172] and pinpointed to the Soderberg potrooms (relative risk = 2.4).[199, 200] Risk increased with increasing duration of employment in this department. Relative risks were 1.0 for less than 1 year, 1.9 for 1

Table 3. BLADDER CANCER RISK AMONG TRUCK DRIVERS

Duration of employment (yr)	Cases*	Controls*	Relative risk†
Never any motor exhaust–related occupation	1353	2724	1.0
<5	74	129	1.2
5–9	32	45	1.4
10–24	33	31	2.1
25+	22	19	2.2
		(χ = 3.93; $P < 0.0001$)	

*Numbers of cases and controls and relative risk according to duration of employment as a truck driver or deliveryman among those first employed at least 50 years before observation. The time of observation was the date of diagnosis for cases and the date of interview for controls. Males with unknown smoking history, duration of employment, or date started employment were excluded.

†Relative to a risk of 1.0 for males never employed in a motor exhaust–related occupation; adjusted for age and smoking.

‡*Data from* Silverman DT, Hoover RN, Mason TJ, *et al*: Motor exhaust–related occupations and bladder cancer. Cancer Res 46:2113–2116, 1986.

to 9 years, 3.0 for 10 to 19 years, 3.2 for 20 to 29 years, and 4.5 for 30 years or more.[200] Armstrong et al[5] used historical data on workplace exposures and found a tenfold risk gradient by exposure level (Table 4). The Soderberg electrolytic reduction process emits coal-tar pitch volatiles,[200] which may contain bladder carcinogens, such as aromatic amines (particularly 2-naphthylamine).[5]

Other Occupations

Bladder cancer risk has been linked to employment as a machinist,[187] but not to a specific type of machine work. Machinists are exposed to mists from oils used as coolants and lubricants in metal machining processes,[183, 207] some of which contain potentially carcinogenic PAHs[183] and nitrosamines.[56]

Increased risk of bladder cancer has also been reported for many other occupational groups: metal workers, printers, chemical workers (other than those involved in manufacturing aromatic amines), hairdressers, dry cleaners, carpenters, construction workers, miners, gas workers, coke plant workers, auto mechanics, petroleum workers, railroad workers, textile workers, tailors, engineers, butchers, clerical workers, cooks and kitchen workers, food processing workers, electricians, gas station attendants, medical workers, pharmacists, glass processors, nursery workers, photographic workers, security guards and watchmen, welders, sailors, stationary fire fighters or furnace operators, stationary engineers, paper and pulp workers, roofers, gardeners, bootblacks, and asbestos workers.[1, 119, 185, 187] Findings for most of these occupations are not as persuasive as those discussed earlier and require corroboration.

The relation between occupation and bladder cancer risk is dynamic.[187] As bladder carcinogens are removed from the workplace and

Table 4. RELATIVE RISKS PREDICTED FOLLOWING 40 YEARS OF EXPOSURE TO TAR VOLATILES*

BSM			BaP		
Concentration (mg/m³)	Relative risk†	95% CI	Concentration (μg/m³)	Relative risk†	95% CI
1.0	8.1	3.8–17.4	10	10.2	4.6–21.8
0.5	4.5	2.40–9.2	5	5.6	2.8–11.4
0.2	2.42	1.56–4.3	2	2.84	1.72–5.2
0.1	1.71	1.28–2.64	1	1.92	1.36–2.15
0.05	1.35	1.14–1.82	0.5	1.46	1.18–2.04
0.02	1.14	1.06–1.33	0.2	1.18	1.07–1.42
0.01	1.07	1.03–1.16	0.1	1.09	1.04–1.21

BSM = benzene-soluble matter; BaP = benzo-a-pyrene; 95% CI = 95% confidence interval.
*Assumes that a minimum of 10 years elapses before an effect of exposure occurs.
†Estimates of risk are relative to a risk of 1.0 for unexposed persons.
From Armstrong BG, Tremblay CG, Cyr D, et al: Estimating the relationship between exposure to tar volatiles and the incidence of bladder cancer in aluminum smelter workers. Scand J Work Environ Health 12:486–493, 1986; with permission.

new chemicals are introduced, changing worker exposures are generating shifts in "high-risk occupations." For example, risks among rubber and leather workers have diminished over time,[117, 163] whereas new high-risk occupations have emerged, such as truck driver and aluminum smelter worker.[184, 214] Thus, occupational bladder cancer continues to be a public health problem, with risks changing over time and from population to population.

Tobacco

Cigarettes

Cigarette smoking is accepted as a cause of human bladder cancer, as demonstrated in more than 30 case-control studies and in ten cohort studies.[6, 16, 18, 32, 34, 42, 67, 75, 92, 94, 97, 135, 158, 170, 176] Typical smokers have two to three times the risk of nonsmokers. Data from correlational studies also are consistent with a smoking–bladder cancer association. In the United States, bladder cancer mortality rates at the state level are highly correlated with per capita cigarette sales,[61] and birth cohort–specific patterns of bladder cancer incidence and mortality parallel the smoking patterns of those cohorts.[3, 81]

In nearly all studies, risk increases with increasing intensity of smoking (packs per day), with relative risk estimates for moderate to heavy smokers usually ranging from about 2.0 to 5.0 as compared with nonsmokers.[6, 18, 32, 34, 42, 75, 92, 170, 176, 208] Some studies report a plateau of risk at moderately high smoking levels; others show rising risk.[6, 42, 75, 92, 176] Longer duration of smoking also correlates with increased risk.[6, 18, 32, 34, 42, 75, 92, 208]

Cessation

Cessation of cigarette smoking leads to an estimated 30% to 60% reduction in bladder cancer risk, as shown in many studies.[92] In some studies, former smokers who stopped smoking many years earlier had the same risk as nonsmokers.[21, 42, 221] Other studies, however, have shown that risk falls markedly within the first 2 to 4 years after stopping, but does not continue to decline thereafter and does not return to the level for nonsmokers.[6, 18, 75, 208] This reduction in risk within the first few years after quitting suggests that cigarette smoke contains agents that act at a late stage of bladder carcinogenesis.[75]

Filtration

Persons who smoke unfiltered cigarettes exclusively appear to face a 35% to 50% higher risk of bladder cancer than those who smoke filtered cigarettes exclusively,[75, 218] yet switching to filtered cigarettes has not been shown to reduce the excess risk[18, 75, 218] (Table 5). This conundrum may mean that people who started smoking unfiltered

Table 5. ESTIMATED RELATIVE RISKS OF BLADDER CANCER, ACCORDING TO USE OF FILTERED AND UNFILTERED CIGARETTES, AMONG CURRENT SMOKERS

Filtered cigarettes/day	Unfiltered cigarettes/day			
	None*	1–19	20–39	>40
None		2.4 (1.3–4.5)	3.1 (1.7–5.6)	3.6 (1.8–6.9)
1–19	1.0	2.4 (1.4–4.1)	2.7 (1.3–5.5)	2.7 (0.8–8.5)
20–39	1.9 (1.1–3.3)	2.1 (1.2–3.7)	3.2 (1.9–5.5)	3.2 (1.5–6.7)
≥40	3.0 (1.4–6.5)	2.9 (1.2–7.0)	3.6 (2.0–6.6)	3.9 (2.1–7.1)
	No. controls, cases			
None		87,56	172,40	61,57
1–19	102,29	165,122	35,28	8,6
20–39	90,48	100,68	328,321	26,26
≥40	24,21	16,15	71,79	73,85

*Reference category is less than 20 filtered cigarettes per day, never smoked unfiltered. Estimates are adjusted for age, sex, race, and duration of smoking. 95% confidence intervals are shown in parentheses.

Data from Hartge P, Silverman D, Hoover R, et al: Changing cigarette habits and bladder cancer risk: A case-control study. J Natl Cancer Inst 78:1119–1125, 1987.

cigarettes start younger, take more puffs of smoke per cigarette, or inhale more deeply. Alternatively, changing from unfiltered to filtered cigarettes actually may exert almost no effect. Interview data may be too inaccurate to capture these subtle differences. If so, the observation that smokers of filtered cigarettes only have a lower risk than smokers of unfiltered cigarettes only needs further evaluation; the observed reduction in risk may have been a chance effect.

Inhalation

Cigarette smokers who inhale deeply may have a greater risk than those who do not,[18, 34, 38] although some studies find no effect.[75, 85, 113] Morrison et al[147] observed 30% to 40% elevation of risk for male cigarette smokers who inhaled deeply as compared with those who inhaled somewhat or not at all.

Black versus Blond Tobacco

Smokers of black tobacco have a risk of bladder cancer two to three times higher than the risk in smokers of blond tobacco.[34, 43, 94, 208, 209] Black tobacco has higher concentrations of aromatic amines, some of which are human bladder carcinogens, than does blond tobacco.[208] Blood levels of 4-aminobiphenyl hemoglobin adducts, as well as adducts

of several other aromatic amines, are higher for smokers of black than of blond tobacco.[17] In addition, the urine of smokers of black tobacco is more mutagenic than is the urine of smokers of blond tobacco.[115, 136]

Pipes, Cigars, and Smokeless Tobacco

Most studies find pipe smokers at moderately elevated risk of bladder cancer (relative risks: 1.3 to 3.9),[32, 73, 85, 97, 113, 137, 147, 189, 216, 220] but some studies find no association.[18, 38, 219] A clear dose-response relationship is rarely seen, but pipe smokers who inhale deeply appear to be at greatest risk.[73, 85]

Weak and inconsistent relationships have been observed between bladder cancer risk and the other forms of tobacco use. Cigar smoking increases risk (relative risks: 1.3 to 2.5) in some studies,[32, 73, 113, 137, 189] but not in others.[18, 38, 85, 97, 101, 147, 216, 219, 220]

Most studies have reported that use of snuff or chewing tobacco does not increase risk of bladder cancer.[18, 38, 73, 85, 137, 220] Snuff users who never smoked cigarettes had excess risk in one study,[189] and users of chewing tobacco had excess risk in two studies.[137, 189]

Dietary Factors

Coffee Drinking

The hypothesis that coffee drinking increases bladder cancer risk was suggested by an unexpected finding in a population-based, case-control study conducted in Massachusetts (relative risk = 1.3 for men and 2.5 for women).[36] Nine subsequent studies indicated little or no overall association in either sex[22, 30, 67, 98, 100, 148, 170] (ref. 167: women only; ref. 189: men only). Eight studies were positive for men, but not for women[14, 32, 33, 62, 74, 85, 130, 219]; four studies were positive for women, but not for men[134, 141, 171] (ref. 188: women only); and four studies suggested an overall positive association without reporting sex-specific risks.[94, 111, 135, 153] In most of the studies reported as positive, however, the relative risk of bladder cancer in typical coffee drinkers compared with non-drinkers has been less than 2, and a regular dose-response relationship has been observed only infrequently,[14, 32, 33, 94, 167, 219] although risk was elevated among drinkers of large amounts of coffee in several studies.[74, 98, 148, 170]

The weakness and inconsistency of the observed associations indicate that if coffee is a bladder carcinogen, it is a weak one. Alternatively, associations between coffee drinking and bladder cancer could reflect residual confounding by cigarette smoking, a strong risk factor for bladder cancer and a strong correlate of coffee drinking.[74, 143, 148] Statistical adjustment is incomplete if smoking categories are too broad or if smoking habits are inaccurately recalled. This residual confounding by smoking can be avoided by evaluating the effect of coffee drinking in lifelong nonsmokers, but few studies have had

enough nonsmokers to estimate this risk with reasonable precision. Of these, some indicated no increased risk associated with coffee drinking,[14, 85, 100, 148] whereas others suggested an increased risk.[30, 33, 74, 135, 170, 171, 189] Of the positive studies that distinguished between men and women in examining the coffee drinking effect, one is positive in both men and women,[170] three are positive in men but not in women,[30, 33, 74] and one is positive in women but not in men.[171]

Artificial Sweeteners

Artificial sweeteners were suggested as potential human bladder carcinogens by the results of animal experiments, particularly of rats exposed to high doses of saccharin in utero and weaned to a saccharin-containing diet.[206] Saccharin did not induce bladder cancer in rats or other animals fed saccharin only after birth.[39]

Extensive epidemiologic investigation has not substantiated a relationship between artificial sweeteners and bladder cancer. Diabetics, who often use artificial sweeteners, have typical bladder cancer mortality rates.[4, 105] Over time, the trend in bladder cancer mortality in England and Wales has not appeared related to saccharin consumption.[3] The Danish population born during World War II, a group with higher in utero saccharin exposure than previous birth cohorts, experienced no excess bladder cancer risk during the first 30 to 35 years of life.[95]

Of the numerous case-control studies measuring the relationship between artificial sweeteners and bladder cancer, most have been negative.[22, 94, 96, 100, 106, 141, 146, 153, 167, 171, 188, 219, 222] One study suggested an increased risk in men (relative risk = 1.6) and a decreased risk in women (relative risk = 0.6).[84, 132] In a large US population–based, case-control study, the relative risk for subjects who had ever used artificial sweeteners was 1.0.[83] A small elevation in risk was seen in very frequent users, but the dose-response pattern was irregular. A positive association was observed in two study subgroups: white male heavy smokers and white female nonsmokers with no known exposure to bladder carcinogens. The reason for these associations is uncertain, however.[82, 212]

It is difficult to separate the effects of saccharin and cyclamates in the United States and Canada because both substances were used extensively in both countries. In England and Japan, where primarily saccharin was used,[147] artificial sweeteners appear unrelated to bladder cancer risk.

The findings of nearly all studies indicate that the use of artificial sweeteners confers little or no excess risk of human bladder cancer. If, in fact, saccharin is a very weak carcinogen, such a low-level effect may not be detectable in epidemiologic studies.[82]

Alcohol Drinking

Most studies of alcohol drinking and bladder cancer have shown no association.[16, 22, 85, 100, 135, 153, 202, 219, 220] Elevated risks related to con-

sumption of specific types of alcoholic beverages have been reported in a few studies,[32, 94, 138, 141, 171, 189] but these findings have not been consistent with respect to type of beverage or sex, and regular dose-response relationships have not been apparent. Thus, the positive findings probably reflect chance or residual confounding by smoking.

Other Dietary Factors

The role of dietary factors in human bladder carcinogenesis is unclear. Dietary supplements of natural and synthetic retinoids inhibit bladder carcinogenesis in laboratory animals,[78] but epidemiologic studies are inconsistent. Milk and other foods that contain vitamin A have been associated with decreased risk of bladder cancer in three case-control studies,[111, 130, 189] but two other case-control studies have not supported this relationship.[171, 204] The use of vitamin A supplements has been associated with decreased risk.[195] Serum levels of retinol, retinol binding protein, and carotenoids appear unrelated to risk.[76, 159, 204] Fruit and vegetable consumption has been associated with lower risk in some studies[32, 111, 130, 135] but not in others.[196]

Bladder cancer risk has been associated with higher intake of cholesterol,[171] with fatty meals,[32] with fried foods,[195] and with relatively high pork and beef consumption.[196] A nearly linear increasing trend in risk with decreasing serum levels of selenium was observed in a nested case-control study in Washington County, Maryland.[76]

Drugs

Analgesics

Case reports first linked heavy consumption of phenacetin-containing analgesics to cancers of the renal pelvis, ureter, and bladder.[90] Fokkens[60] reported that Dutch subjects who had a lifetime consumption of at least 2 kg had a relative risk of 4.1 as compared with incidental users or nonusers. McCredie et al[121, 122] found a relative risk of 2.0 in Australian women 45 to 85 years of age who had a lifetime consumption of at least 1 kg. Piper et al[168] reported a relative risk of 6.5 in US women aged 20 to 44 years who had used phenacetin-containing compounds for at least 30 days in a year. Despite these fairly strong associations, a regular gradient in risk with increasing dose was demonstrated in only one study.[122] Further study will be limited because most western countries no longer allow phenacetin-containing analgesics to be sold.

Acetaminophen, an analgesic popular since the 1970s, showed no increased risk in two studies,[121, 168] but it may be too soon for any excess to be detectable.

Cyclophosphamide and Chlornaphazine

Cyclophosphamide, an alkylating agent used to treat both malignant and nonmalignant diseases since the early 1950s, has been linked

to risk of bladder cancer in many case reports and case series.[91, 112] Cyclophosphamide produces bladder tumors in both rats and mice.[91] Patients with non-Hodgkin's lymphoma treated with cyclophosphamide experienced a sevenfold risk of bladder cancer in a Danish study.[165] A report of bladder cancer risk among patients with non-Hodgkin's lymphoma who received chemotherapy, based on data from the SEER program and the Connecticut Tumor Registry, also was positive (observed/expected = 1.7).[203] Additional groups of patients, such as long-term survivors of breast cancer who were treated with cyclophosphamide as adjuvant chemotherapy, should be studied to measure more precisely the carcinogenic risk associated with use of this important antineoplastic drug.

In the 1960s, the antineoplastic drug chlornaphazine was linked to the development of bladder cancer.[201] Chlornaphazine is related chemically to 2-naphthylamine. This drug was never used in the United States and probably is not widely used elsewhere.[89]

Urologic Conditions

Urinary Tract Infection

Urinary bladder infection has been linked to risk of bladder cancer in several case-control studies[51, 85, 102, 110, 167, 220] but not all.[107] In the United States, Kantor et al[102] found an increased risk in both men and women; subjects with a history of at least three infections had a relative risk of 2.0, as compared with those with no infections. In addition, bladder infection was more strongly associated with squamous cell than with transitional cell cancer, a striking parallel to the relation between schistosomiasis and squamous cell bladder cancer. Because the dates of the bladder infections were not obtained in most of the reported studies, it is possible that the occurrence or diagnosis of infections may have been the consequence of early bladder cancer, rather than a cause of the disease.

Urinary Stasis

If carcinogens are present in urine, urinary retention or stasis might increase the risk of developing bladder cancer by increasing the duration of contact of the carcinogens with the bladder mucosa.[162] Although urinary stasis has not been investigated directly as a risk factor, several findings are consistent with the hypothesis that stasis is related to risk. First, medical conditions that cause stasis, such as benign prostatic hypertrophy, have been associated with increased risk,[51, 58, 139] though it is uncertain whether these conditions preceded the diagnosis of bladder cancer. Second, infrequent micturition and high urine concentration, both of which increase urine contact with bladder epithelium, were more prevalent in high-risk areas of Israel than in low-risk areas.[13] Third, the upper hemisphere of the bladder (dome), which has less

contact with urine than the rest of the bladder, is a relatively infrequent site of bladder tumors.[162] Fourth, dogs exposed to 2-naphthylamine do not develop tumors in bladders that have not been in contact with urine.[123] Finally, urine itself appears to be a promoter of bladder carcinogenesis in the rat.[160, 173]

Schistosoma haematobium

S. haematobium infection has been believed to increase risk of bladder cancer for 80 years,[59] and yet convincing epidemiologic data supporting this association are lacking. It is true that the proportional incidence of bladder cancer is high in countries with endemic schistosomiasis.[198] Also, squamous cell tumors are more common in endemic areas: in Egypt, more than 70% of bladder cancers are squamous cell[198]; in the United States, 2% are. On the other hand, bladder cancer incidence rates appear similar in areas of Africa where schistosomiasis is endemic, infrequent, or absent.[164]

In two studies, more bladder cancer patients had schistosome infection than did other hospital patients.[64, 151] In series of cases from South Africa and Zambia, *S. haematobium* ova were found in higher proportions of patients with squamous cell than with transitional cell tumors.[9, 79] Monkeys infected with *S. haematobium* develop bladder tumors,[108] but these are transitional cell. Hamsters infected with *S. haematobium* develop squamous metaplasia in the bladder.[54]

Schistosomiasis infection could predispose patients to bladder cancer if chronic inflammation by calcific ova and urinary retention caused by infection affects the absorption of carcinogens from the urine.[27] Alternatively, the urine of patients infected with *S. haematobium* or bacteria may harbor carcinogenic nitroso compounds,[198] or the schistosoma antigen might depress the immunocompetence of infected patients.[126]

Radiation

Ionizing radiation causes bladder cancer, but this exposure is so rare that it contributes very little to bladder cancer incidence in the general population. Women who received therapeutic pelvic radiation for dysfunctional uterine bleeding appear to have a two to four fold risk of bladder cancer.[88, 211] High-dose radiotherapy was associated with a fourfold risk of bladder cancer in a large, international study of cervical cancer patients treated with radiation.[11] Women under the age of 55 years when first treated had higher risks than older women. Risk increased with increasing dose to the bladder, and with time since exposure, with the relative risk reaching 8.7 for patients treated at least 20 years earlier.

Radioactive iodine (iodine-131) exposure has also been associated with elevated bladder cancer risk. A threefold risk was found among

women who had a thyroid uptake procedure with iodine-131.[167] A cohort of patients treated with high-dose iodine-131 for thyroid cancer also experienced excess risk.[53]

Follow-up of atomic bomb survivors in Hiroshima and Nagasaki revealed a dose-response relationship between radiation exposure and bladder cancer mortality.[154] Two groups of workers at nuclear installations in the United Kingdom had excess bladder cancer mortality,[87, 191] but no excess was seen in a group of US nuclear workers.[66]

Drinking Water and Fluid Intake

Chlorination by-products in drinking water were first linked to bladder cancer risk by ecologic studies[156] and later by two case-control studies based on death certificates.[40]

In three investigations, detailed information was available on water quality and temporal aspects of exposure. These studies support the association between chlorination by-product levels in drinking water sources and bladder cancer risk. In Washington County, Maryland, residents supplied with chlorinated surface water had higher bladder cancer incidence rates than did those who consumed unchlorinated deep well water (relative risks were 1.8 and 1.6 for men and women, respectively).[215] In the NCI study conducted in ten areas of the United States, risk increased with level of intake of beverages made with tap water.[19] The gradient was restricted to subjects with at least 40 years of exposure to chlorinated surface water and was not observed among long-term consumers of nonchlorinated ground water. Among subjects whose residences were served by a chlorinated surface water source for at least 60 years, a relative risk of 2.0 was estimated for heavy consumers compared to low consumers of tap water. In a study in Massachusetts, residents of communities supplied with chlorinated drinking water experienced higher bladder cancer mortality than did those of communities exposed to water containing lower concentrations of chlorination by-products (mortality odds ratio = 1.6).[225]

A relation between exposure to high levels of arsenic in artesian well water and bladder cancer mortality has been suggested by surveys conducted in an endemic area of chronic arsenic toxicity, manifested by skin cancer and blackfoot disease in Taiwan.[28, 29, 217]

Total fluid intake also may be related to bladder cancer risk, but the results have been equivocal. Increased total fluid consumption has been associated with decreased risk,[51] with a positive trend in risk,[19, 32, 98] and with no excess risk.[190, 220]

Hair Dyes

Use of hair dyes has been examined in relation to bladder cancer risk because hairdressers and barbers have been reported to be at

elevated risk.[35] In addition, findings from mutagenicity tests and animal experiments indicate that some compounds in hair dyes are mutagens and possible bladder carcinogens, and persons who dye their hair appear to excrete dye compounds in their urine.[72] Results of several epidemiologic studies, however, are negative.[72]

Familial Occurrence

Familial predisposition to bladder cancer has been seen in clinical case reports and in a few case-control studies.[20, 103, 167] In the largest case-control study to date,[103] familial risks were especially high among those with environmental exposures, such as heavy cigarette smoking, suggesting genetic and environmental interactions.

PREVENTIVE MEASURES

Avoidance of cigarette smoking is the most effective means available to prevent bladder cancer. In the United States, half of bladder cancer cases in men and one third in women are attributable to smoking, larger fractions than for any other single factor.[92] A further preventive measure would be curtailment of hazardous occupational exposures.

Screening offers some promise as a potential method to control bladder cancer. In general, a cancer screening program can be successful only if, first, an adequate screening test is available. Second, the prevalence of the detectable preclinical phase of the disease must be high. Third, a treatment must be available that is more effective for the screen-detected disease than for otherwise similar, routinely diagnosed disease.[144] It is uncertain whether all these conditions are met for bladder cancer.

Cytologic examination of the urine may be a satisfactory screening test, with a sensitivity of about 75%[86, 104] and a specificity above 95%,[104] possibly as high as 99.9%.[86] Furthermore, this test is inexpensive, convenient, and risk-free. Testing for asymptomatic hematuria also has been investigated as a method of screening for bladder cancer, but a single test is not sensitive enough, and repeated testing at short intervals[128, 129] would yield too many false positives.

Too few preclinical bladder cancers are prevalent in the general population for large-scale screening programs to be rewarding.[142] On the other hand, certain occupational groups probably have high enough prevalence to justify screening as a bladder cancer control measure.[104]

The natural history of preclinical bladder cancer is poorly understood. Screen-detected cases of most types of cancer typically have better survival than routinely diagnosed cases, even if screening confers no benefit in terms of reduced mortality from the disease.[144] For bladder cancer, the opposite pattern may obtain, with worse survival in screen-detected cases.[181] Screening for bladder cancer seems to detect prefer-

entially cases with prognostically unfavorable histologic appearance.[57, 104] Neither of these findings, by themselves, would negate the possible value of screening. However, they suggest that the gains may be small, and that particular care is needed in designing and evaluating bladder cancer screening programs.[86]

Lastly, the effectiveness of the treatment of bladder cancer is uncertain. No data are available on the relative value of treating bladder cancer "early," as detected by screening, or "late," as it comes to medical attention as a result of symptoms. In summary, research on screening probably should be focused on intervention trials among high-risk groups to determine whether urine cytology, alone or in combination with other screening methods, leads to a reduction in mortality from bladder cancer.[205]

SUMMARY

Approximately 49,000 persons in the United States develop bladder cancer each year, and about 9700 die of it. White men face a lifetime risk of almost 3%; white women and black men face a risk of about 1%, and black women, about 0.5%.

Cigarette smoking is accepted widely as a cause of bladder cancer. Smoking accounts for about half of bladder cancer diagnosed among men and about one third of that among women. Moderate to heavy smokers typically show a two to five fold risk of bladder cancer, compared with persons who never smoked. When cigarette smokers quit smoking, their bladder cancer risk falls measurably within 2 to 4 years, but probably does not continue to decline with increasing years since quitting and does not appear to return to the baseline level of nonsmokers.

Occupational exposure to certain aromatic amines causes human bladder cancer. Clear evidence of bladder cancer risk also is apparent for a small number of occupational groups: dye workers, rubber workers, leather workers, painters, truck drivers, and aluminum workers. Many other occupational groups have been reported to have increased bladder cancer risk, but evidence for these is not as strong.

Coffee drinking has been studied extensively as a potential risk factor, but the inconsistency of the observed associations suggests that the relationship is either quite weak, noncausal, or dependent in a complex way on unmeasured factors. Artificial sweeteners confer little or no excess bladder cancer risk. Alcohol consumption apparently does not affect risk either. Consumption of fruits, vegetables, and foods high in vitamin A have been suggested as possible protective factors; consumption of high-fat foods, pork, and beef have been suggested as possible risk factors. Further epidemiologic research is needed to elucidate the role of diet in human bladder carcinogenesis.

Less common risk factors for bladder cancer include ionizing radiation, cyclophosphamide use, and abuse of phenacetin-containing

analgesics. Schistosomiasis infection may contribute substantially to the bladder cancer burden in Egypt and elsewhere, though not in the United States. Other urinary tract infections that are common worldwide may increase risk, but additional research is necessary to confirm that the infections preceded the occurrence of the bladder cancer.

Long-term consumption of drinking water containing chlorination by-products, total fluid volume, and urinary stasis have all been suggested to influence risk. Because these exposures are difficult to measure and to separate from one another, a clear conclusion regarding them cannot be drawn at this time.

Large-scale screening of the general population for early bladder cancer is not feasible yet. An intervention trial is needed to assess whether screening by urine cytology, alone or in combination with other methods, reduces mortality in a group at high risk for bladder cancer.

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